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PATENT

Attorney Docket No.: 010692-004532US

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

on September 22, 2003

TOWNSEND and TOWNSEND and CREW LLP

By Masta M. Martines

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Stephen R. Gorfine

Application No.: Filed Herewith

Filed: Herewith

For: NITRIC OXIDE DONOR COMPOSITION AND METHOD FOR TREATMENT OF ANAL DISORDERS

Examiner: To be assigned

Art Unit:

To be assigned

Declaration of Inventor Pursuant to MPEP §608.01(p) Regarding Sameness of Amendatory Material Previously

Incorporated by Reference

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

I, Stephen R. Gorfine, am the named and true inventor of the subject matter disclosed and claimed in the above-referenced patent application.

The references which are the source of the above amendatory material were incorporated by reference to exemplify the role and pathways by which "NO mediates the anorectal inhibitory reflex in animals and man." The above references each disclose L-arginine to be an important part of the pathway to NO formation and L-arginine in particular to be an NO precursor which releases NO under physiological treatment conditions.

I declare that the following recital of the Preliminary Amendment filed herewith sets forth amendatory material which consists of the same subject matter as that indicated to be incorporated by reference: Application No.: Filed Herewith

Attorney Docket No.: 010692-004532US

The role of nitric oxide in relaxation of the internal anal sphincter (IAS) in response to the rectoanal reflex has been studied in the opossum by others (see, Rattan S., Sarkar A., Chakder S., Gastroenterology, (1992 Jul), 103(1):43-50). They monitored resting pressures in the IAS using low-compliance continuously perfused catheters and reported the following.

L-NG-nitro-arginine (L-NNA), a NO-synthase inhibitor, caused significant dose-dependent suppression of the decrease in resting pressures in the IAS in response to the reflex mimicked by the rectal balloon distention. IAS relaxation in response not only to rectoanal reflex but also to other neural stimuli such as sacral nerve stimulation, local intramural stimulation, and the nicotinic ganglionic stimulant 1,1-dimethyl-4-phenylpiperazinium was also blocked by an NO-synthase inhibitor. The suppression of the neurally mediated IAS relaxation by L-NNA was stereoselective; D-NNA had no effect on the relaxation. The suppression of the rectoanal reflexinduced IAS relaxation by L-NNA was completely reversed by NO precursor L-arginine stereoselectively as D-arginine failed to reverse the suppressed IAS relaxation. The decrease in the resting pressure of the IAS caused by sodium nitroprusside was modified neither by the neurotoxin tetrodotoxin nor by L-NNA. Furthermore, the inhibitor of NO synthase did not modify the decrease in the resting pressure of the IAS by the direct-acting beta-adrenoceptor agonist isoproterenol. It was concluded that NO or a NO-like substance is an important mediator of IAS relaxation in response to noradrenergic, noncholinergic nerve stimulation.

Another study by others on the release of nitric oxide by activation of nonadrenergic noncholinergic neurons of internal anal sphincter has also been reported (see, Chakder S., Rattan S., Am J. Physiol, (1993 Jan), 264(1 Pt 1):G7-12.). This study investigated the direct release of nitric oxide (NO) in response to the stimulation of nonadrenergic noncholinergic (NANC) nerves. Isolated smooth muscle strips of the opossum (Didelphis virginiana) internal anal sphincter (IAS) were used. This study reported the following:

Electrical field stimulation (EFS) of these strips using the appropriate parameters was reported to cause a frequency-dependent fall in the resting tone of the IAS. The chemiluminescence method was used in the study to measure the release of NO. The stimulation of NANC neurons by the nicotinic stimulant 1,1-dimethyl-4-phenylpiperazinium (DMPP) and EFS caused IAS relaxation with an accompanying release of NO. The study found pretreatment of the smooth muscles

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with the neurotoxin tetrodotoxin and the NO-synthase inhibitor NG-nitro-L-arginine (L-NNA) abolished the release of NO and the fall in the resting tension of IAS in response to lower frequencies of EFS and DMPP. Addition of the NO precursor L-arginine reversed to control levels of the loss of the release of NO and the IAS relaxation in the presence of L-NNA. Again, the effect of L-NNA and L-arginine on NO release and IAS relaxation was stereoselective. D-NNA and Darginine had no significant effect. The release of NO from IAS smooth muscle strips caused by vasoactive intestinal polypeptide was also abolished by L-NNA. However, both isoproterenol and atrial natriuretic factor caused IAS relaxation without any increase in NO release. These investigations show that NO is directly released in response to the stimulation of gut NANC inhibitory neurons.

An additional study of nerve mediated relaxation of the human internal anal sphincter investigated the role of nitric oxide. See, O'Kelly T., Brading A., Mortensen N., Gut, (1993 May) 34(5):689-93. This reference concerns whether nitric oxide (NO) is the non-adrenergic, non-cholinergic neurotransmitter which is released by enteric inhibitory nerves to mediate relaxation of the human internal anal sphincter. Isolated muscle strips were mounted in a superfusion organ bath so as to record their isometric tension. This study reported the following:

An exogenous donor of NO, sodium nitroprusside, relaxed the strips in a dose dependent manner. presence of atropine and guanethidine, transmural field stimulation produced relaxations. relaxations were sensitive to tetrodotoxin. relaxations were also inhibited in a concentration dependent and stereospecific manner by antagonists of NO synthase; completely by L-nitroarginine and partially by L-N-monomethyl arginine. These inhibitory effects were reversed by L-arginine. Darginine did not reverse them. The relaxations were abolished by the nitric oxide scavenger, oxyhaemoglobin, but not methaemoglobin. The O'Kelly, et al. findings strongly indicated that NO is, or is very closely associated with, the non-adrenergic, noncholinergic neurotransmitter which mediates the neurogenic relaxation of the human internal anal sphincter.

The subject matter of the above recitals closely correspond to the Abstracts for each of the above cited references. The recitals have in particular been amended to make it clear that the inventors are not describing their own work. True copies of each of the Abstracts for the above cited references are enclosed as Exhibits

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A, B, and C, respectfully. A true copy of the earliest priority document (i.e., the specification of U.S. Patent No. U.S. Application No. 08/250,555, filed on May 27, 1994) is also enclosed as Exhibit D. This document incorporates the above cited references in the first paragraph of p. 5. This application is a continuation application of the co-pending U.S. Patent Application No. 10/021,168 (Exhibit E) which recites the above references at p. 5, lines 3-10, and incorporates them by reference at p. 9, lines 1-3.

In view of the foregoing, I declare and respectfully submit that the above recited amendatory material belongs to the same material incorporated by reference in the referencing application.

I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Date:

Stephen R. Gorfing

59058075 v3



DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled NITRIC OXIDE DONOR COMPOSITION AND METHOD FOR TREATMENT OF ANAL DISORDERS, the specification of which is attached hereto.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed: NONE

I hereby claim the benefit under Title 35, United States Code, 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application: U.S. Application Serial No. 08/250,555, filed May 27, 1994 and entitled "A Pharmacological Preparation for the Treatment of Anal Disorders".

I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and to file and prosecute any corresponding foreign applications, including any international applications under the Patent Cooperation Treaty or the European Patent Convention: J. David Wharton, Reg. No. 25,717; Don M. Bradley, Reg. No. 22,412; Michael B. Hurd, Reg. No. 32,241; Joan Optican Herman, Reg. No. 31,968; Patrick A. Lujin, Reg. No. 35,260; Michael J. Gross, Reg. No. 35,528; and D. Bartley Eppenauer, Reg. No. 35,499, telephone number (816) 474-6550. Address all correspondence to: SHOOK, HARDY & BACON P.C., One Kansas City Place, 1200 Main Street, Kansas City, Missouri 64105-2118.

10983861

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor's signature:

Stephen R. Gorfine

Date

Residence: Citizenship:

Post Office Address:

New York county, New York United States of America

1215 Fifth Avenue

New York, New York 10029



10/021,168

DISORDERS

December 11, 2001

Stephen R. Gorfine

NITRIC OXIDE DONOR

TREATMENT OF ANAL

Please type a plus sign (+) inside this box

POWER OF ATTORNEY OR

AUTHORIZATION OF AGENT

PTO/SB/81 (02-01)

Approved for use through 10/31/2002. OMB 0651-0035 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

COMPOSITION AND METHOD FOR

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Filing Date

Title

Applicati n Number

First Named Inventor

Not yet assigned **Group Art Unit** Not yet assigned **Examiner Name** 010692-004531US **Attorney Docket Number** I hereby appoint: Practitioners at Customer Number 20350 ☐ Practitioner(s) named below: Registration_N Name as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith. Please change the correspondence address for the above-identified application to: The above-mentioned Customer Number. ☐ Practitioners at Customer Number Firm or Individual Name Address Address City State ZIP Country Fax Telephone I am the: Applicant/Inventor. Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96). SIGNATURE of Applicant or Assignee of Record TOHN J. CHANDLER Name Signature EBRUARY 200 Z NOTE: Signatures of all the inventors or assignees of record of the ntire interest or their repres ntative(s) are required. Submit multiple forms if more than one signature is required, see below*.

Approved for use through 10/31/2002. OMB 0651-0031
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Attorney Docket No. 010692-004531US

STATEMENT UNDER 37 CFR 3.73(b)			
Applicant/Patent Owner: Stephen R. Gorfine			
Application No./Patent No.: 10/021,168 Filed/Issue Date: December 11, 2001 Entitled: NITRIC OXIDE DONOR COMPOSITION AND METHOD FOR TREATMENT OF ANAL DISORDERS			
Cellegy Pharmaceuticals, Inc. , a corporation			
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)			
states that it is:			
1. the assignee of the entire right, title, and interest; or			
2. an assignee of an undivided part interest			
in the patent application/patent identified above by virtue of either:			
A. An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the Patent and Trademark Office at Reel, Frame, or for which a copy thereof is attached.			
OR ·			
B. A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:			
 From: <u>Stephen R. Gorfine</u> To: <u>Neptune Pharmaceutical Corporation</u> The document was recorded in the United States Patent and Trademark Office at Reel <u>7374</u>, Frame <u>0516</u>, or for which a copy thereof is attached. 			
 From: Neptune Pharmaceutical Corporation To: Cellegy Pharmaceuticals, Inc. The document was recorded in the United States Patent and Trademark Office at Reel 9052, Frame 0861, or for which a copy thereof is attached. 			
3. From:			
The document was recorded in the United States Patent and Trademark Office at Reel, Frame, or for which a copy thereof is attached.			
Additional documents in the chain of title are listed on a supplemental sheet.			
Copies of assignments or other documents in the chain of title are attached. [NOTE: A separate copy (i.e., the original assignment document or a true copy of the original document) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.8]			
The undersigned (whose title is supplied below) is empowered to sign this statement on behalf of the assignee.			
4 FEBRUARY 2002 Date Signature			
TottN J_ CI+ANDLEN_ Typed or printed name			
UP CORPORATE DE VELOPHENT			
Title			

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

UNITED STATES DEPARTMENT OF COMMERCE Patent and Trademark Office ASSISTANT SECRETARY AND COMMISSIONER OF PATENTS AND TRADEMARKS 00 4520 W. Washington D.C. 20231

Washington, D.C. 20231

MAY 27, 1998

PTAS

TOWNSEND AND TOWNSEND AND CREW LLP MARGARET A. POWERS TWO EMBARCADERO CENTER, 8TH FLOOR SAN FRANCISCO, CA 94111-3834



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THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILMICORY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER m **≥** REFERENCED BELCW.

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RECORDATION DATE: 03/27/1998

REEL/FRAME: 9052/0861

NUMBER OF PAGES: 6

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

NEPTUNE PHARMACEUTICAL CORPORATION DOC DATE: 12/31/1997

ASSIGNEE:

CELLEGY PHARMACEUTICALS, INC. 1065 EAST HILLSDALE BOULEVARD, SUITE 418

FOSTER CITY, CALIFORNIA 94404

SERIAL NUMBER: 08970447 PATENT NUMBER:

SERIAL NUMBER: 08250555

PATENT NUMBER: 5504117

SERIAL NUMBER: 08666264 PATENT NUMBER: 5693676

FILING DATE: 11/14/1997

ISSUE DATE:

FILING DATE: 05/27/1994 ISSUE DATE: 04/02/1996

FILING DATE: 06/20/1996 ISSUE DATE: 12/02/1997

9052/0861 PAGE 2

MAYA BENNETT, EXAMINER ASSIGNMENT DIVISION OFFICE OF PUBLIC RECORDS

Rev. 6-93)	10067621	1 SHEET Patent and Trademark	OTTICE	
To the Honorable Asst. Commissio	ner for Patents. Please rec	ord the attached original documents or copy thereof.		
1. Name of conveying party(ies):		2. Name and address of receiving party(ies):		
Neptune Pharmaceutical Corpor	ation	Name: Cellegy Pharmaceuticals, Inc.		
Additional name(s) of conveying party(ies) a	ttached? Yes X No	Internal Address:		
		Street Address: 1065 East Hillsdale Boulevard, Suite 41	В	
3. Nature of conveyance: X Assignment Security Agreement Other:	Merger Change of Name	City: Foster City State: Clifornia Zip: 94404 MAR 2 7 1998 RECEIPT ACCT NO. DOV		
Execution Date: December 31.	1997			
		Additional name(s) & address(es) attached? Yes	x No	
If this document is being filed to	ogether with a new applica	B. Patent No.(s) 5,504,117		
5. Name and address of party to concerning document should be	whom correspondence e mailed:	6. Total number of applications and patents involved: 3]	
		x Charge any additional fees associated with this pa	per or ny	
	$\overline{}$	8. Deposit account number: 20-1430		
	70447			
581 80.00 CH	DO NOT U	SE THIS SPACE		
9. Statement and signature. To the best of my knowledge of the original document. Margaret A. Powers Name of Person Signing Atty. Reg. No. 39,804	Morat	<u>March 23, 1998</u> Date	e copy	
10. Change Correspondence Addr	ess to that of Part 57 X	Y s No		
OMB N . 0651-0011 (exp. 4/94)				
	over cheet information to:	•		
	1. Name of conveying party(ies): Neptune Pharmaceutical Corpor Additional name(s) of conveying party(ies) at 3. Nature of conveyance: X Assignment Security Agreement Other: Execution Date: December 31, 4. Application number(s) or patent if this document is being filed to A. Patent Application No.(s 5. Name and address of party to concerning document should be concerning to the concerning document should be concerning to the concerning document	To the Honorable Asst. Commissioner for Patents. Please rec 1. Name of conveying party(ies): Neptune Pharmaceutical Corporation Mage	To the Honorable Asst. Commissioner for Patents. Please record the attached original documents or conv thereof. 1. Name of conveying partylies): Name of conveying partylies): Name of conveying partylies): Name: Cellegy Pharmaceuticals, Inc. Internal Address: Street Address: 1065 East Hillsdale Boulevard, Suite 41: 3. Nature of conveyance: X Assignment	

Form PTO-1595
Recordation Form Cover Sheet
Patents Only
Page 2

- Additional name(s) of conveying party(ies): (Continued from Page 1)
- 2. Additional name(s) and address(es) of receiving party(ies): (Continued from Page 1)
- Additional application number(s) or patent number(s): (Continued from Page 1)
 - A. Patent Application No.(s)

B. Patent No.(s) 5,693,676

PATENT ASSIGNMENT

For good and valuable consideration, the receipt of which is hereby acknowledged, the person(s) named below (referred to as "ASSIGNOR" whether singular or plural) has sold, assigned, and transferred and does hereby seil, assign, and transfer to Cellegy Pharmaceuticals, Inc., a California corporation, having a place of business at 1065 East Hillsdale Boulevard, Suite 418, Foster City, CA 94404 ("ASSIGNEE"), for itself and its successors, transferrees, and assignees, the entire worldwide right, title, and interest in all inventions and improvements [("SUBJECT MATTER") that are disclosed in United States Letters Patent listed on Schedule A strached hereto and the patent applications listed on Schedule B attached hereto, together with any reissue, extension, improvement, division, commutation or commutation-in-part of any thereof, in the U.S. or worldwide, and all rights of priority resulting from the filing in the United States of the patents or patent applications identified on Schedule A or H.

ASSIGNOR agrees that ASSIGNEE may apply for and receive patents for SUBJECT MATTER in ASSIGNEE's own pame.

ASSIGNOR agrees to do the following, when requested, and withour further consideration, in order to carry out the intent of this Assignment: (1) execute all caths, assignments, powers of attorney, applications, and other papers necessary or desirable to fully secure to ASSIGNEE the rights, titles and interests herein conveyed; (2) communicate to ASSIGNEE all known facts relating to the SUBJECT MATTER; and (3) generally do all lawful acts that ASSIGNEE shall reasonably consider desirable for vesting in ASSIGNEE the rights, titles, and interests herein conveyed. ASSIGNOR further agrees to provide any successor, assign, or legal representative of ASSIGNEE with the benefits and assistance provided to ASSIGNEE hereunder.

ASSIGNOR represents that ASSIGNOR has the rights, titles, and interests to convey as set forth herein, and covenants with ASSIGNEE that ASSIGNOR has made or will make hereafter no assignment, grant, mortgage, license, or other agreement affecting the rights, titles, and interests herein conveyed.

This Assignment may be executed in one or more counterparts, each of which shall be deemed an original and all of which may be taken together as one and the same Assignment.

Name and Signature

Date of Date Declaration

Signature Executed By This Person

Neptuna Pharmaceutical Corporation

By September 10, 1997 December 90, 1997

OPENSELLE. GROEFFE TA

SCHEDULEA

Patents

Country	Patent No.	Date of Patent	Title "
U.S.A.	5,504,117	4/2/95	Pharmacologic Preparation for the Treatment of Anal Disorders
.a.R.U	5,693,676	12/2/97	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders

SCHEDULER

Patent Applications

			•
Country	Serial/Appl. No.	Filing Date	Title
Istaei	113,448	4/20/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
China	95190687.9	4/10/95	Nitrie Oxide Donor Composition and Method for Treatment of Anal Disorders
Korca	700442/1996	4/10/95 ·	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
Mexico	960386	4/10/95	Nitrie Oxide Donor Composition and Method for Treatment of Anal Disorders
Singapore	96 00491-6	4/10/95	Nitrie Oxide Donor Composition and Method for Treatment of Anal Disorders
Canada	2168247	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
Japan	500835/96	4/10/95	Nime Oxide Donor Composition and Method for Treatment of Anal Disorders
EPC	95916264.5	4/10/95	Nitric Oxide Donor Composition and Method for Treatment of Anal Disorders
U.S.A.	08/970,447	11/14/97	Nitric Oxide Donor Composition for Treatment of Anal Disorders

County of New York	
eppeared Strophen R. Goothne personally known to of satisfactory evidence to be the person whose name is subsert acknowledged to me that (he/she) executed the same in [his/her [his/her] signature on the instrument the person, or the emity satisfactory, executed the instrument.	bed to the within instrument and authorized capacity, and that by
Notery Scal NINA L. KLISCSIK Note	ry
Notary Public, State of New York No. 4602348	
Outsified in Suffolk Country JAN 31,1/94	
and the same of th	